REMARKS

Withdrawal of Claims 5-20 is Improper

Applicants have amended claims 5-20 to remove the improper claim formatting. Applicants note that, if the Examiner believed that claims 5-20 were in improper dependent form, the Examiner should have objected to these claims, rather than withdraw these claims. *See* MPEP §608.01(n)(II). Applicants respectfully request that the Examiner remove any objection to currently amended claims 5-20 and place them under consideration for substantive examination.

Support for the Claim Amendments

Applicants have amended claim 1 to better capture the envisioned commercial embodiments. The specification fully supports the amended claims in at least paragraphs 0068, 0086, 0088 and 0091 and Figures 1 and 3 of the published application (Pregrant Publication No. 2007/0196336). For example, paragraph 0068 indicates that the shuttle vector may comprise a stuffer sequence, and Figure 3 and paragraph 0088 provide one embodiment of the stuffer sequence being a portion of a lambda sequence. Figure 3 also shows that the shuttle vector used in one embodiment (pVec9) is about 10.57kb in length, exclusive of the gene encoding the target protein. Paragraph 0091 and Figure 1 demonstrate the insertion of pVec9 (at least 10.57kb) into the herpes simplex genome construct (T-BAC) using Cre recombinase. Paragraph 0086 highlights that T-BAC is about 157.7 kb. Thus, paragraph 0091 and Figure 1 show that the herpes simplex construct, after insertion of the shuttle vector is about 168 kb in length, exclusive of the gene encoding the target gene of interest. Accordingly, the specification fully supports the amendments to claim 1.

Claim Objections

Applicants have amended claim 1 to correct the typographical error as the Examiner suggested. Applicants thank the Examiner for her helpful comment and suggestion.

Obviousness Rejection

The Office Action of 28 July 2008 rejected claims 1-4 as allegedly obvious under U.S. Published Application No. 2002/0110543 ("Chiocca"), Buchholz, F. and Stewart, A., *Nature Biotechnology*, 19:1047-1052 (2001) ("Buchholz") and Krisky, D. *et al., Gene Therapy*, 5:1517-1530 (1998) ("Krisky"). Applicants respectfully disagree.

Applicants assert that the cited art, alone or in combination fails to establish a *prima facie* case of obviousness against the presently claimed invention. To establish a *prima facie* case of obviousness, the cited references must teach every limitation of the currently claimed invention, *In re Royka* 490 F.2d 981, 985 (C.C.P.A. 1974). Applicants assert that the cited art as a whole fails to teach each and every claim limitation. In addition, there must exist a reasonable expectation of success in combining the references, and this expectation of success should be found in the references as well. *In re Vaeck* 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants assert that the cited references fail to provide one of skill in the art with a reasonable expectation of success for combining or altering the references in the manner prescribed in the office action.

Applicants have amended claim 1 to specify that the shuttle vector comprises stuffer sequence. As described in the specification, a stuffer sequence refers to a DNA sequence which does not have any unnecessary action on virus growth and can be contained in the shuttle vector. The shuttle vector is then inserted into the HSV genome by using the Cre-loxP system in order to extend the length of the HSV genome. Since the construct will no longer take on the form of a virus when the length of genome reaches a size of about 168 kb or larger, a stuffer sequence of an appropriate length will not allow the production of a viral particle. Viral particle production would then only be possible if the HSV genome is excised from the construct using the Flp-FRT system. The claimed methods make it easy to differentiate viruses that successfully obtained the target recombination from those that failed with the target recombination, resulting in eliminating a lot of time and effort to identify the target recombinant virus

On the other hand, Chiocca does not teach or suggest a use of the stuffer sequence. Furthermore, Chiocca also does not teach or suggest a use of the HSV genome having a suitable length for effectively identifying the virus containing the target recombinant HSV genome in light with the mechanism of production of the HSV virus. At most, Chiocca discloses a method and a system for producing HSV (vectors) containing transgenes of interest. In particular, the Office relies upon the "HsvQuik system" as shown in Example 2 (Fig. 7) of Chiocca for the basis of the obviousness rejection. The "HsvQuik system" consists of two components: a bacterial artificial chromosome (BAC) clone containing the backbone HSV-1 sequence ("fHSVQuik-1", ~160 kb); and a transgene-transfer plasmid ("pTransfer", 2 kb) (see Fig. 7 and [0186] in Chiocca). In the HsvQuik system, the pTransfer is inserted into the FRT site of fHSVQuik-1 by using the Flp-FRT system to give a "fHsvQ1-X." Thus, it is clear that the fHsvQ1-X construct, with the pTransfer being inserted into the FRT site of fHSVQuik-1 is only ~162k nucleotides (*i.e.*, ~160 kb +2 kb) including the nucleotides encoding the target protein. Since the length of the fHsvQ1-X construct is much less than about 170kb, the HSV constructs of Chiocca can be produced, even before any elements of the construct have been excised with the Cre-loxP system. Thus, the methods of Chiocca result in spending more time and effort to identify the viruses containing the target recombinant construction than the present invention. Accordingly the method of the present invention in the amended claim 1 (to 19) wherein the stuffer sequence is used is greatly different from the method disclosed in Chiocca, and is not obvious in view of Chiocca.

Buchholz was cited by Examiner in relation to claim 2 to state that Cre recombinase can be expressed in culture. In addition, Krisky was cited by Examiner in relation to claim 4 to state that the deletion or inactivation of ICP 47 enhances the effectiveness of the transgene designed to increase tumor immunity. Neither Buchholz nor Krisky teaches the use of the stuffer sequence and the use of the HSV genome having suitable length for effectively identifying the virus containing the target recombinant construction.

Because the combination of cited references fails to teach all of the elements of the claimed invention, and because the combination of references fails to provide a reasonable expectation of success, Applicants assert that the cited references fail to render obvious the claimed invention. Moreover, Applicants assert that the Office Action fails to articulate precisely why one of skill in the art would alter or combine the references in the manner prescribed in the Office Action. Accordingly, Applicants assert that the references fail to establish a prima facie case of obviousness. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

CONCLUSION

Applicants have amended the claims to better capture the envisioned commercial embodiments and to correct typographical errors and to format the revise the claim to comply with proper claim format. Applicants have also presented arguments regarding the non-obviousness of the claimed invention. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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